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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/920,653	08/03/2001	Masaharu Noda	31671-173164	6043

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EXAMINER	
TON, THAIAN N	
ART UNIT	PAPER NUMBER
1632	

DATE MAILED: 05/05/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/920,653	NODA ET AL.	
	Examiner	Art Unit	
	Thai-An N Ton	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *26 January 2004*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 3-34* is/are pending in the application.

4a) Of the above claim(s) *5-23,25-34* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,3,4 and 24* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicants' Amendment, filed 1/26/04, has been entered. Claim 2 has been cancelled. Claims 1 and 3-34 are pending. Claims 5-23 and 25-34 are withdrawn from further consideration pursuant to 37 CFR 1.142(b) as being drawn to a nonelected groups, there being no allowable generic or linking claim. Election was made **without** traverse in Paper No. 14. Claims 1, 3, 4 and 24 are under current examination.

Specification

The objection to the disclosure is withdrawn in view of Applicants' amendment to the specification.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

The prior rejection of claims 1-4 and 24 under 35 U.S.C. 112, first paragraph, is maintained for reasons of record because the specification, while being enabling for a mouse whose genome comprises a homozygous disruption of the exon 1 of the endogenous Na_v2 gene, wherein the disruption results in a phenotype of normal salt intake under water sufficient conditions, when compared to wild-type mice, but

shows an increase of hypertonic saline under water and salt-depleted conditions, when compared to a wild-type mouse and methods of screening using the knockout mouse, the specification does not reasonably provide enablement for a null mutant non-human animal characterized in showing salt intake behavior similar to that of wild-type animals under water-sufficient conditions and showing much more intakes of hypertonic saline compared with wild-type animals under water and salt-depleted conditions, and methods of using the same. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

Applicants argue that the instant specification is enabling. Applicants point to Mullins (cited by the Examiner in the prior Office action) for support by stating that, "As is clear from the above citation [*i.e.,* Mullins], germ transmission is not an essential component in producing an animal model using murine other including mice, but rather the direction of research in the technical field is directed to produce ES cells. Therefore, it is respectfully submitted that one cannot conclude that ES cells are not available in the species other than mouse." See p. 12, last ¶ of Applicants' Response.

This is not found to be persuasive. The Examiner has provided Moreadith, Mullins and Pera in support of the unpredictability in state of the art of ES cells. Both Moreadith and Pera clearly state that although putative ES cells exist for

other species, these putative cells have not been shown to give rise to germline tissue, which is an art-recognized property of ES cells. See Moreadith, p. 214 and Pera, both cited in the prior Office action. It is noted that Applicants' quotation of Mullins is directed to transgenesis in species other than mice. Mullins clearly states that microinjection, which results in the random integration of the transgene, is used in species other than mice. See *Abstract*. The production of the knockout mice taught by the specification require targeting of a specific gene [Na_v2], which require ES cells, as supported by Mullins, would, "[P]ermit the directed integration of the transgene to a specific region of the chromosome via homologous recombination. With the advent of homologous recombination, the researcher is able to insertionally inactivate, replace, or introduce subtle alterations to the endogenous gene of interest." It is reiterated that some of the claims recite that the null mutant non-human animal is a rodent. See claim 3. It is noted that the breadth of the term "rodent" encompasses various that include beavers and squirrels. See Encyclopedia Britannica, http://www.search.eb.com/dictionary. As stated previously, mammalian ES cells have not been described from species other than mouse; as such, the claimed null mutant rodents are not enabled.Applicants have failed to provide evidence or teachings which are persuasive with regard to ES cells from species other than mice, and the state of the art, as stated in the prior Office action, clearly teaches that ES cell technology is limited to mice at present.

Accordingly, it is maintained that only mouse ES cells were available for the production of the claimed null mutant mice.

Applicants argue that the Examiner's position is not in accordance with regard to those skilled in the genetic engineering art because persons skill in the art are not only working on the study of the correspondence in mice between disrupted genes and it is clear that the significance and goal of the genetic engineering art is to elucidate the genetic characteristics of humans by investigating as a representative the genetic characteristics of mice, which are readily available and easily engineered. Applicants argue that it is a common assumption that a genetic characteristic newly found applies to animals other than mice. See p. 13, ¶ 1-3.

This is not found to be persuasive. The enabled scope of the instant invention is based upon the unpredictable state of the transgenic knockout art. The issue at hand is not, as asserted by Applicants, that working on the correspondence in mice between the disruption of a particular gene and the elucidation of genetic characteristics of humans is not significant or a goal of those who study genetic engineering. The claimed invention is directed to knockout animals, and the specific working examples are directed to null mutant mice. The phenotype associated with the mice presented in the working example is a phenotype of normal salt intake under water sufficient conditions, when compared to wild-type mice, but shows an increase of hypertonic saline under water and salt-depleted conditions. The breadth of the claims is directed to non-human animals, however,

as stated previously, ES cells were not available to produce the null mutant non-human animals, as claimed, and further, it would be unpredictable that a particular disruption (in the instant case, in the Na_v2 gene) would result in the same phenotype in any non-human animal. See Moreadith, Sanford, cited in the prior Office action. Further, Applicants have not provided any evidence or teachings of record to show that one could predictably knock out a particular gene and achieve a particular phenotype. The Examiner has provided the state of the art, which clearly shows the unpredictability of both the ES cells art and the transgenic art, with particular regard to the unpredictability in the resulting phenotype. One of skill in the art must be able to both make and use the claimed invention for the breadth claimed, however, one of skill would not be able to predict the phenotype of a null-mutant non-human animal for the reasons stated previously. Thus, one of skill would not be able to both make and use the claimed invention.

Applicants point to various patents to show evidence that the term "non-human animal" is enabling. See p. 14 of Applicants' Response.

This is not found to be persuasive for the reasons listed above with regard to the unpredictability in the ES cell art and the transgenic art. Furthermore, each application is judged upon its own merits.

Accordingly, in view of the quantity of experimentation necessary for the production and use of null mutant non-human animals, for the breadth claimed, the lack or direction or guidance, as well as absence of working examples, provided by

the specification for the production and use of null-mutant non-human animals comprising a disruption in the Na_v2 knockout mammals, other than the exemplified Na_v2 knockout mouse, wherein the disruption is in exon 1 of the Na_v2 gene, the unpredictable and undeveloped state of the art for the production of knockout non-human animals, particularly with respect to the phenotypic effect, and the breadth of the claims encompasses null-mutant non-human animals, it would have required undue experimentation for one of skill in the art to make and/or use the claimed non-human animals and methods of using the same.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 1, 3, 4 and 24 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 1 is unclear. The claim recites, "which shows salt intake behavior ..." in line 3 of the claim. It is unclear if "which" refers to the genes or the animal. Claims 3, 4, and 24 depend from claim 1.

The prior rejection of claim 24 is maintained. The claim is drawn to a method of screening a material that promotes or suppresses the function or the expression of a protein acting as a sensor of extracellular sodium ion level

characterized in using the non-human animal according to claim 1, a transgenic non-human animal which excessively expresses a protein acting as a sensor of extracellular sodium ion level. The claim fails to provide an active step for screening the material. It merely states "using" a non-human animal according to claim 1 and another transgenic non-human animal. This does not provide clear, active steps for the method.

Conclusion

No claim is allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Thaian N. Ton whose telephone number is (571) 272-0736. The Examiner can normally be reached on Monday through Friday from 8:00 to 5:00 (Eastern Standard Time), with alternating Fridays off. Should the Examiner be unavailable, inquiries should be directed to Amy Nelson, Acting SPE of Art Unit 1632, at (571) 272-0804. Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is (703) 872-9306.

TNT

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